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Disentangling the effects of peripheral inflammatory markers on brain functional connectivity

Neil A Harrison^{1,2}

AFFILIATIONS

1. Cardiff University Brain Research Imaging Centre (CUBRIC), Department of Psychology, Cardiff University, Maindy Road, Cardiff, CF24 4HQ, United Kingdom;
2. Division of Psychological Medicine and Neuroscience, Department of Medicine, Cardiff University, Cardiff, CF24 4HQ, United Kingdom

CORRESPONDING AUTHOR

Prof Neil Harrison, MB BS, PhD, Cardiff University, Cardiff University Brain Research Imaging Centre (CUBRIC), Maindy Road, Cardiff, CF 24 4HQ, United Kingdom. Phone: +44 (0)2920 876785, email: HarrisonN4@cardiff.ac.uk

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Discovery of the role of inflammatory processes in mental health and ill-health, particularly disorders of mood, represents a major advance in understanding in psychiatry, and with it the opportunity to develop/ repurpose immunotherapies for real patient benefit (1). In the context of acute inflammation, pro-inflammatory mediators (e.g. cytokines) rapidly activate parallel neural and humoral immune-brain communicatory pathways to perturb local (e.g. neurotransmitter) as well as distributed networks of neural activity to impair mood, motivation and cognition (2). Recent studies are beginning to suggest that similar mechanisms may also be at play in the context of chronic low-level inflammation (3). In rodents, chronic stress leads to migration of immature monocytes into corticolimbic brain regions implicated in the regulation of mood and behavior. These cells appear necessary for the emergence of anxiety-like behaviors (4). However, to date no study has investigated how these cells relate to brain function in humans. In this issue of Biological Psychiatry, Nusslock et al. (5) address these issues in two well powered studies that combine molecular (and in the second study cellular) inflammatory markers with resting-state (rs) functional MRI (fMRI).

This study has a number of important strengths and implications. Firstly, by repeating their analyses in two independent cohorts, Nusslock et al (5) demonstrate that a composite index of inflammation (combining C-reactive protein (CRP), Interleukin (IL)-6, IL-10 and tumor necrosis factor (TNF)-alpha) negatively scales with functional connectivity within the emotional regulation network across both cohorts i.e. individuals with a higher inflammatory index showed weaker function connectivity within this network. In the second cohort (performed with a more advanced multi-band fMRI sequence) this inflammatory index also scaled negatively with functional connectivity within the central executive network, a network implicated in the cognitive regulation of emotion, behavior and thought. Interestingly, the design of their second study allowed them to additionally investigate associations with circulating immune cells and test the specific hypothesis that higher levels of circulating classical (CD14⁺⁺/CD16⁻) monocytes, that are homologous to immature (Ly-6c high) monocytes linked to stress-induced anxiety in mice, would be associated with lower functional connectivity within brain networks linked to emotional regulation. Their data supported this hypothesis, with classical monocytes negatively scaling with functional connectivity within both the emotion-regulation and central executive networks in keeping with rodent data regarding monocytes trafficking to the brain. Importantly, this relationship was not observed for any of the other leukocyte subsets tested.

Another important feature of Nusslock et al's (5) study was that it was performed in two cohorts that differed across a range of socioeconomic, age, sex, and environmental factors supporting the ecological validity and generalizability of their findings. In the first study, participants were 25-year-old African-Americans living in rural Georgia in households defined as 'working poor'. Of the 90 participants 52% were female and 46% lived below the federal poverty line. The second study included 82 African-American youth (67% female) with a mean age of 13.9 years living in Chicago, Illinois. In this cohort, all reported good health (no history of chronic medical or psychiatric illness and free of prescription medications for 3 months) and 22% lived in households below the federal poverty line. Furthermore, identification of a consistent relationship between an index of peripheral inflammation and functional connectivity within an emotional control network despite

marked differences in age suggests that this linkage is relatively stable across development. Previous epidemiological studies have linked raised inflammatory markers (IL-6) in early life (at 9 years) to an increased risk of later depression (and psychotic experiences) aged 18 years (6). Though not tested here, it would be intriguing to know whether changes in functional connectivity mediate this association, or whether they reflect a preclinical vulnerability marker for the later emergence of psychiatric symptoms.

Nusslock et al's (5) finding of an association between circulating classical monocytes and decreased functional connectivity within emotion regulation networks in the second ostensibly healthy adolescent cohort has potentially important implications. It raises questions about how broadly monocyte trafficking to the brain influences human brain function in apparent health and the importance of this mechanism in psychiatric disorders, particularly post-traumatic stress, depression and anxiety. The concept that immune cell trafficking to the CNS can influence normal brain function and neuronal connectivity is not without precedent. For example, preclinical studies have suggested that meningeal resident T-lymphocytes are necessary to support neuronal connectivity and social behavior (7). Further, as mentioned earlier, the preclinical literature implicates monocyte trafficking to the brain in the development of stress-induced anxiety (4). However, to date the pre-clinical literature implicating monocyte trafficking to the brain in stress-induced anxiety is largely restricted to models that include repeat exposure to severe social stress (using the repeated social defeat model), a model that is associated with marked increases in sympathetic outflow which acts on the bone marrow and spleen to bias myeloid precursor cells (particularly monocytes) toward a glucocorticoid-resistant and primed lineage. Furthermore, even in this context signaling from the CNS must occur for monocytes to traffic to the CNS (4). Nusslock et al's (5) important findings suggest a potentially broader relationship between monocyte trafficking and brain function in humans. This finding will undoubtedly stimulate future studies aiming to clarify the range, magnitude and duration of stressors that activate this pathway.

Two further (negative) findings from Nusslock et al's (5) study deserve further consideration and interpretation within the broader inflammation-imaging literature. Firstly, their prediction of a positive association between peripheral inflammation and functional connectivity within the anterior salience network (which included nodes within bilateral anterior insula, dorsal anterior cingulate and middle frontal gyri). Interestingly, though this prediction was not supported in either of their study cohorts, activation of the insula and anterior cingulate cortex (which form the primary anchors for the salience network) are a common feature of studies using robust and even relatively mild acute inflammatory challenges (2). In this context they have been interpreted as representing activation of a neurally mediated immune-brain communicatory pathways that projects to posterior insula with forward projections to anterior insula providing a consciously accessible representation of inflammation frequently experienced as fatigue (2). Though the basis for this discrepancy remains incompletely understood (perhaps due to an absence of interoceptive surprise in the context of chronic low-level inflammation) it has also been observed in meta-analysis comparing studies using acute inflammatory challenges versus observational inflammatory studies (8). This meta-analysis also highlighted activations within regions encompassing the broader salience network including amygdala, striatum (particularly ventral regions), substantia nigra, hypothalamus, dorsomedial thalamus and dorsal anterior cingulate as well

as some regions such as the sub-genual cingulate and hippocampus/parahippocampus that fall within the default mode or limbic networks that appear relatively commonly activated across both acute challenge and observational inflammatory studies (2,8). Furthermore, some of these structures appear to play relatively specific roles in discrete aspects of inflammation-associated behavioral change. For example, actions on the ventral striatum have been linked to impaired reward sensitivity, and anterior insula in heightened sensitivity to punishment and subjective experience of fatigue (2).

In their currently study, Nusslock et al (5) adopted a hypothesis driven approach and consequently constrained their analysis to a restricted group of networks principally associated with emotion regulation. This powerful and commonly adopted approach has been associated with a number of other notable successes within the field. For example, the demonstration that in major depression, circulating C-reactive protein (CRP) negatively scales with functional connectivity of the ventral striatum and medial pre-frontal reward processing areas (3) and that this scaling of ventral striatal to medial pre-frontal functional connectivity mediates the relationship between CRP and experienced anhedonia (3). However, restriction of analyses to pre-selected functional networks as opposed to adoption of an unconstrained data-driven approach (9) risks providing an incomplete snapshot of how inflammatory mediators modulate whole brain connectivity and can introduce heterogeneity (through variation in network selection and definition) that likely contributes to some of the inconsistencies in the literature. For example, though Nusslock et al did not identify an association between peripheral inflammation and default mode connectivity in either of their cohorts, another recent study in 98 middle aged adults reported that IL-6 positively scaled with the functional connectivity of the sub-genual cingulate component of the default mode and negatively with the dorsal medial pre-frontal cortex component at robust statistically corrected thresholds (9) (though these authors did not investigate the relationship of IL-6 with any other functional brain networks).

As the field matures and larger data sets become available it will be important to comprehensively characterize how broadly peripheral inflammatory markers influence brain functional connectivity networks and disentangle which discrete inflammatory mediators e.g. cytokines and/or cellular processes such as classical monocytes mediate these effects. Disrupted functional brain connectivity is commonly reported across a range of psychiatric disorders (many of which are also linked to raised inflammatory markers). Clarification of the role of immune mediators in this process will not only aid understanding of the pathogenesis of these disorders but may also help in the development of novel immunotherapies.

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